

What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide comprising a sequence of amino acids substantially
5 corresponding to the amino acid sequence set out in SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.8 or SEQ ID NO. 9, said polypeptide having the ability to stimulate vascular permeability or proliferation of endothelial cells, or a fragment or analogue thereof which has the ability to
10 stimulate at least one biological activity selected from the group consisting of angiogenesis, vascular permeability, endothelial cell proliferation, differentiation, migration or survival, or which has the ability to bind to endothelial cells, but is unable to
15 stimulate at least one of said biological activities.

2. A nucleic acid molecule according to claim 1, wherein said nucleic acid molecule comprises a nucleic acid sequence which encodes the amino acid sequence

Pro-Xaa-Cys-Val-Xaa-Xaa-Xaa-Arg-Cys-Xaa-Gly-Cys-Cys
5 (SEQ ID NO.2).

3. A nucleic acid molecule according to claim 1, wherein said endothelial cells are selected from the group consisting of vascular endothelial cells and lymphatic endothelial cells.

4. A nucleic acid molecule according to claim 1, which is a genomic DNA.

5. A nucleic acid molecule according to claim 1, which is a cDNA.

6. A nucleic acid molecule according to claim 5, which comprises the nucleic acid sequence of SEQ ID NO.1, SEQ ID NO.4, SEQ ID NO.6, SEQ ID NO.7, or a DNA sequence

which hybridizes to one of the foregoing sequences under
5 stringent conditions.

7. A nucleic acid molecule according to claim 6,
which comprises the nucleic acid sequence of SEQ ID NO.4.

8. A nucleic acid molecule according to claim 1,
which encodes a polypeptide which has the ability to
stimulate vascular permeability or proliferation of
endothelial cells.

9. A nucleic acid molecule according to claim 1,
which encodes a polypeptide comprising amino acid residues
64 through 172 of SEQ ID NO:3 or amino acid residues 93
through 201 of SEQ ID NO:5.

10. A nucleic acid molecule according to claim 9,
wherein said polypeptide further comprises an affinity tag
peptide sequence.

11. A nucleic acid molecule according to claim 1,
which encodes a polypeptide which has the ability to bind
to endothelial cells but is unable to stimulate
endothelial cell proliferation.

12. A nucleic acid molecule according to claim 11,
wherein said endothelial cells are selected from the group
consisting of vascular endothelial cells and lymphatic
endothelial cells.

13. A nucleic acid molecule according to claim 1,
wherein said nucleic acid molecule is a human DNA
molecule.

14. A vector comprising a nucleic acid according to
claim 1.

15. A host cell transformed or transformed with a vector according to claim 14.

16. An isolated polypeptide which comprises a sequence of amino acids substantially corresponding to the amino acid sequence set out in SEQ ID NO.3, SEQ ID NO.5, SEQ ID NO.8 or SEQ ID NO. 9, said polypeptide having the ability to stimulate vascular permeability or proliferation of endothelial cells, or a fragment or analogue thereof which has the ability to stimulate at least one endothelial cell biological activity selected from the group consisting of cell proliferation, cell differentiation, cell migration, cell survival and vascular permeability, or which has the ability to bind to endothelial cells but is unable to stimulate at least one of said biological activities.

17. A polypeptide according to claim 16, wherein said polypeptide comprises the amino acid sequence
Pro-Xaa-Cys-Val-Xaa-Xaa-Xaa-Arg-Cys-Xaa-Gly-Cys-Cys
(SEQ ID NO.2).

18. A polypeptide according to claim 16, wherein said endothelial cells are selected from the group consisting of vascular endothelial cells and lymphatic endothelial cells.

19. A polypeptide according to Claim 16, which comprises a sequence of amino acids substantially corresponding to SEQ ID NO:3 or SEQ ID NO:5.

20. A polypeptide according to Claim 19, which comprises a sequence of amino acids substantially corresponding to SEQ ID NO 5.

21. A polypeptide according to claim 16, which has the ability to stimulate proliferation of endothelial cells.

22. A polypeptide according to claim 16, which has the ability to induce endothelial cell differentiation.

23. A polypeptide according to claim 16, which has the ability to induce vascular permeability.

24. A polypeptide according to Claim 16, comprising amino acid residues 64 through 172 of SEQ ID NO:3 or 93 through 201 of SEQ ID NO:5.

25. A polypeptide according to claim 24, further comprising an affinity tag peptide sequence.

26. A polypeptide according to claim 16, which has the ability to bind to endothelial cells but is unable to stimulate proliferation of endothelial cells.

27. A polypeptide according to claim 26, wherein said endothelial cells are selected from the group consisting of vascular endothelial cells and lymphatic endothelial cells.

28. A polypeptide according to claim 16, wherein said polypeptide is a human protein.

29. An antibody specifically reactive with a polypeptide according to claim 16.

30. An antibody according to claim 29, wherein said antibody is a polyclonal antibody.

31. An antibody according to claim 29, wherein said antibody is a monoclonal antibody.

32. An antibody according to claim 29, wherein said antibody is labelled with a detectable label.

33. A method of making a polypeptide according to claim 16, said method comprising the steps of:

5 culturing a host cell transformed or transfected with a vector comprising a nucleic acid sequence encoding said polypeptide operably associated with a promoter sequence such that the nucleic acid sequence encoding said polypeptide is expressed; and

isolating said polypeptide from said host cell or from a growth medium in which said host cell is cultured.

34. A method of isolation of polypeptide according to claim 16, said method comprising the step of exposing a cell which expresses said polypeptide to heparin to facilitate release of the polypeptide from the cell, and purifying the thus-released polypeptide.

35. A method of making a vector capable of expressing a polypeptide encoded by a nucleic acid molecule according to claim 1, said method comprising inserting said nucleic acid molecule into a vector in a position in which said nucleic acid molecule is
5 operatively connected with at least one promoter.

36. A vector comprising an anti-sense nucleotide sequence, said anti-sense nucleotide sequence being complementary to at least a part of a VEGF-D genomic DNA sequence or a VEGF-D RNA sequence or a cDNA sequence which
5 encodes VEGF-D or a fragment or analogue thereof which promotes at least one bioactivity selected from vascular permeability, proliferation of endothelial cells and endothelial cell differentiation, whereby said vector can be used to inhibit said at least one bioactivity.

37. A method of stimulating endothelial cell proliferation comprising contacting endothelial cells with an effective endothelial cell proliferation stimulating amount of a polypeptide according to claim 16.

38. A method according to claim 37, wherein said endothelial cells are selected from the group consisting of vascular endothelial cells and lymphatic endothelial cells.

39. A method of stimulating at least one bioactivity selected from endothelial cell proliferation, endothelial cell differentiation and vascular permeability, *in vivo* in a mammal, said method comprising administering to said
5 mammal an effective bioactivity stimulating amount of a polypeptide according to claim 16, which has the ability to stimulate said at least one bioactivity.

40. A method according to Claim 39, wherein said polypeptide comprises amino acid residues 64 through 172 of SEQ ID NO:3 or amino acid residues 93 through 201 of SEQ ID NO:5.

41. A method according to Claim 39, wherein lymphatic vessel endothelial cell proliferation is stimulated.

42. A method of stimulating at least one bioactivity selected from angiogenesis and neovascularization in a mammal, said method comprising the step of administering to said mammal an effective angiogenesis or
5 neovascularization stimulating amount of a polypeptide according to claim 16, said polypeptide having the ability to stimulate endothelial cell proliferation.

43. A method according to Claim 42, wherein said polypeptide comprises amino acid residues 64 through 172 of SEQ ID NO:3 or amino acid residues 93 through 201 of SEQ ID NO:5.

44. A method according to claim 43, wherein said polypeptide further comprises an affinity tag peptide sequence.

45. A method according claim 32, further comprising co-administering at least one substance selected from the group consisting of VEGF, VEGF-B, VEGF-C, PlGF, PDGF, FGF and heparin.

46. A method of inhibiting a bioactivity selected from angiogenesis and neovascularization in a mammal, said method comprising the step of administering to said mammal an effective angiogenesis or neovascularization inhibiting
5 amount of a VEGF-D antagonist according to claim 70.

47. A method according to claim 46, wherein said VEGF-D antagonist comprises an antibody specific to VEGF-D.

48. A method according to claim 46, wherein said VEGF-D antagonist comprises a polypeptide which binds to endothelial cells but which is unable to stimulate at least one biological activity selected from proliferation
5 of endothelial cells, endothelial cell differentiation and vascular permeability.

49. A method according to claim 48, wherein said endothelial cells are selected from the group consisting of vascular endothelial cells and lymphatic endothelial cells.

50. A method of inhibiting VEGF-D expression in a mammal comprising the step of transforming target cells expressing VEGF-D with a vector according to Claim 36.

51. A pharmaceutical composition comprising a polypeptide according to claim 16, and a pharmaceutically acceptable carrier or adjuvant.

52. A pharmaceutical composition according to claim 51, further comprising at least one substance selected from the group consisting of VEGF, VEGF-B, VEGF-C, PlGF, PDGF, FGF and heparin.

53. A pharmaceutical composition comprising an antibody according to claim 29, and a pharmaceutically acceptable carrier or adjuvant.

54. A pharmaceutical composition according to Claim 53, wherein said antibody is a monoclonal antibody.

55. A protein dimer comprising a first polypeptide according to claim 16, and a second polypeptide.

56. A protein dimer according to Claim 55, wherein said protein dimer is a homodimer in which the second polypeptide is identical to the first polypeptide.

57. A protein dimer according to claim 55, wherein said protein dimer is a heterodimer in which the second polypeptide is selected from VEGF, VEGF-B, VEGF-C, PlGF and PDGF.

58. A method of detecting a polypeptide according to claim 16 in a biological sample, said method comprising the step of contacting the sample with a reagent capable of binding said polypeptide, and detecting the occurrence of binding of said reagent.

59. A method according to claim 58, wherein said reagent comprises an antibody according to claim 29.

60. A method of modulating vascular permeability in a mammal, said method comprising administering to said mammal an effective vascular permeability modulating amount of a polypeptide according to claim 16 or an antibody thereto.

61. A method according to claim 60, comprising administering to said mammal a polypeptide according to claim 16, having the ability to stimulate endothelial cell proliferation.

62. A method according to claim 60, comprising administering to said mammal a polypeptide according to claim 16, which has the ability to bind to endothelial cells, but which is unable to stimulate endothelial cell proliferation.

63. A method of activation of at least one receptor selected from the group consisting of VEGF receptor 2 and VEGF receptor 3, said method comprising the step of exposing cells bearing said receptor to an effective receptor activating dose of a polypeptide according to claim 16.

64. A method according to claim 63, wherein said method is carried out *in vivo*.

65. A method according to claim 63, wherein said method is carried out *in vitro*.

66. A diagnostic or prognostic test kit comprising a specific binding reagent for a polypeptide according to claim 16, and means for detecting binding of said reagent.

67. A test kit according to claim 66, wherein said specific binding reagent comprises an antibody to said polypeptide.

68. A diagnostic or prognostic test kit comprising a pair of primers specific to a nucleotide sequence according to claim 1, operatively coupled to a polymerase, whereby said polymerase is enabled to selectively amplify the nucleotide sequence from a DNA sample.

69. A method of detecting aberrations in VEGF-D gene structure in a test subject comprising the steps of:

providing a DNA sample from said test subject;

5 contacting said sample with a set of primers specific to a nucleotide sequence according to claim 1, operatively coupled to a polymerase and selectively amplifying said nucleotide sequence from said sample by polymerase chain reaction; and

10 comparing the nucleotide sequence of the amplified nucleotide sequence from said sample with a nucleotide sequence as set forth in SEQ ID NO:1 or SEQ ID NO:4.

70. A VEGF-D antagonist having the capability to inhibit at least one biological activity induced by VEGF-D selected from vascular permeability, endothelial cell proliferation and endothelial cell differentiation, said antagonist binding to VEGF-D or to a VEGF-D receptor, but
5 being less able than VEGF-D to stimulate said at least one biological activity.

71. A VEGF-D antagonist according to claim 70, wherein said antagonist comprises an antibody which selectively binds VEGF-D.

72. A VEGF-D antagonist according to claim 71, wherein said antibody is a monoclonal antibody.

73. A VEGF-D antagonist according to claim 71, wherein said antagonist comprises a VEGF-D polypeptide fragment or analogue which binds to a VEGF-D receptor, but is less able to stimulate said at least one biological activity.

74. A method of improving pulmonary blood circulation and/or gas exchange in a mammal, said method comprising administering to said mammal an effective blood circulation and/or gas exchange improving amount of a polypeptide according to claim 16.

76. A method of treating fluid accumulation in the heart and/or lung due to increases in vascular permeability in a mammal, said method comprising administering to said mammal an effective vascular permeability decreasing amount of an antagonist according to claim 70.

76. A method of treating an intestinal malabsorption syndrome in a patient suffering therefrom, said method comprising administering to said patient an effective intestinal blood circulation and/or vascular permeability increasing amount of a polypeptide according to claim 16.